REMARKS

After entry of this amendment, claims 70-85, 87-96, and 98-105 will be pending for the Examiner's review and consideration. Claims 86 and 97 have been canceled. Applicants reserve the right to prosecute the canceled claims and subject matter in one or more related applications. Claims 70-74, 87, 88, 93 and 95 have been amended. Specifically, claims 70, 71, 87 and 88 have been amended to specify that the pharmaceutically acceptable salt of hydromorphone is hydrochloride salt, the hydrophobic polymer is acrylic and methacrylic acid polymers and copolymers, and the hydrophobic fusible carrier is fatty acids, fatty alcohols, or their mixtures. Claims 72-74, 93 and 95 have been similarly amended. Claims 70 and 87 have also been amended to remove any recitation relating to the comparison to an immediate-release hydromorphone dosage form. New claims 98-105 have been added. Support for the new claims and claim amendments can be found in the originally-filed application at, *e.g.*, Exs. 17, 18, 19, 24 and 26. For the Examiner's convenience, a table summarizing the pharmacokinetic parameters disclosed in Exs. 24 and 26 is enclosed as Exhibit A to this Amendment. No new matter has been added.

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested.

I. THE WRITTEN DESCRIPTION REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 70-97 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleges that the specification does not provide disclosure which recites a range for AUC, C_{max}, and T_{max} or percent comparison to an immediate release formulation of the same dosage; that the only immediate release formulation tested was Dilaudid®, 8 mg tablet, and that there is no basis for concluding that all immediate release formulations would have the same AUC, C_{max}, and T_{max} as Dilaudid®. For the following reasons, Applicants respectfully disagree.

The test for sufficiency of written description is whether the disclosure of the application "reasonably conveys to the artisan that the inventor had possession" of the

claimed subject matter. *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983); *accord Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); *see also, Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985).

Claims 70 and 71 recite in part a sustained-release hydromorphone dosage form which provides the recited range of *in vivo* plasma concentrations (*e.g.*, AUC, C_{max}, and T_{max}) in the fasted state and in the fed state, respectively. Claims 87 and 88 recite a method of preparing a sustained-release hydromorphone dosage form which provides the recited range of *in vivo* plasma concentrations (*e.g.*, AUC, C_{max}, and T_{max}) in the fasted state and in the fed state, respectively. Claims 98 and 99 recite a method of treating a patient with a sustained-release hydromorphone dosage form which provides the recited range of *in vivo* plasma concentrations (*e.g.*, AUC, C_{max}, and T_{max}) in the fasted state and in the fed state, respectively.

With regard to the claimed range of AUC, C_{max}, and T_{max} in the specification, the Examiner appeared to require that the range itself must be explicitly disclosed in the specification. In response, Applicants submit that the present specification, through its examples, discloses not only the pharmacokinetic parameters that define the claimed range, but additional pharmacokinetic parameters that fall within the range (*see* Exhibit A). Therefore, although the range itself is not explicitly recited in the specification, one skilled in the art would understand that Applicants had possession of the claimed range at the time the application was filed.

The Examiner cited *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1328 (Fed. Cir. 2000) to support the argument that the range itself must be disclosed. However, the pending claims are distinguishable from the claims at issue in *Faulding* for a number of reasons. First, in *Faulding*, the specification not only does not provide the C_{max}/C_{24} ratio, a limitation in the claims at issue, but, as the Court found, does not suggest to one skilled in the art that the C_{max}/C_{24} ratio is an important defining quality of the formulation or even motivate one to *calculate* the ratio from the C_{max} and C_{24} data disclosed (emphasis added). *Faulding*, 230 F.3d at 1327. In contrast, the instant application has disclosed the endpoints of the claimed range for AUC, C_{max} and T_{max}, as well as additional values that are within the range. In other words, one skilled in the art *needs not calculate* the range from two discrete sets of data (emphasis added). Moreover, the claimed range for AUC, C_{max} and T_{max} is relatively narrow. Second, in *Faulding*, while the claims recite a C_{max}/C_{24} limitation of greater than 2, the specification contains examples in which the C_{max}/C_{24} is greater than 2, as well as

examples in which the C_{max}/C_{24} is less than 2. *Id.* at 1326. In the instant application, Applicants did not exclude any pharmacokinetic data resulted from the 8 mg hydromorphone hydrochloride formulations in the working examples. A copy of the *Faulding* opinion is enclosed in the Supplemental Information Disclosure Statement as reference D09 submitted herewith.

As such, Applicants submit that the specification has reasonably conveyed to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed.

With regard to the comparison to the pharmacokinetics of Dilaudid®, although Applicants disagree with the Examiner's rejections, solely to expedite prosecution of the application, Applicants have amended claims 70 and 87 so that they no longer recite the comparisons of the pharmacokinetic parameters between the claimed sustained release formulation and the immediate release formulation. As such, the rejection is believed to be moot and should be withdrawn.

Accordingly, claims 70-85, 87-96, 98 and 99 are believed to comply with the written description requirement and the rejection should be withdrawn.

II. THE ENABLEMENT REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 70-97 are rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification, while being enabling for the specific formulations prepared which resulted in the specific AUC, C_{max} and T_{max} observed, allegedly does not reasonably provide enablement for any extruded blend divided into a unit dosage form containing the claimed hydrophobic materials and hydrophobic fusible carriers and 8 mg of hydromorphone or salt thereof. Specifically, the Examiner alleges that the predictability in the art appears to be low, that there is not indication as what other formulation would result in the claimed AUC, C_{max}, or T_{max}, that the claims are broad in that there are numerous possible combinations of the claimed excipients and oral dosage forms, and that one of ordinary skill in the art would be required to do undue experimentation in order to determine what other formulation containing 8 mg of hydromorphone or a salt thereof would result in an AUC, C_{max}, or T_{max} falling within the scope of the claims. For the following reasons, Applicants respectfully disagree.

The enablement requirement refers to the requirement of 35 U.S.C. § 112, first paragraph, that the specification describe (1) how to make and (2) how to use the invention. *See* M.P.E.P. § 2164. The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *United States v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). By definition, undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 443 F.2d 1386, 1392, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). Enablement is not precluded even if some experimentation is necessary, provided the experimentation required is merely routine. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Jackson*, 217 U.S.P.Q. 804, 807 (Bd. Pat. App. & Inter. 1982)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983).

Claims 70 and 71 recite a sustained-release dosage form comprising an extruded blend of hydromorphone hydrochloride, one or more hydrophobic polymers, and one or more hydrophobic fusible carriers having a melting point from about 30°C to about 200°C. Claims 87 and 88 recite a method of preparing a sustained-release dosage form comprising an extruded blend of hydromorphone hydrochloride, one or more hydrophobic polymers, and one or more hydrophobic fusible carriers having a melting point from about 30°C to about 200°C. Claims 98 and 99 recite a method of treating a patient with a sustained-release dosage form comprising an extruded blend of hydromorphone hydrochloride, one or more hydrophobic polymers, and one or more hydrophobic fusible carriers having a melting point from about 30°C to about 200°C. These claims further specify that the hydrophobic polymers are acrylic and methacrylic acid polymers and copolymers, and the hydrophobic fusible carriers are fatty acids, fatty alcohols, or mixtures thereof. In addition, the sustained-release dosage form provides the recited *in vivo* plasma concentration values (*i.e.*, AUC, C_{max}, and T_{max}) in the fasted and fed states.

The specification, through working examples, discloses a number of controlled-release hydromorphone dosage form comprising the specifically claimed hydrophobic polymers (*i.e.*, acrylic and methacrylic acid polymers and copolymers) and hydrophobic fusible carriers having a melting point from about 30°C to about 200°C (*i.e.*, fatty acids or

fatty alcohols) (*see* Exs. 17, 18 and 19). The specification also teaches how to make such hydromorphone dosage form, how to treat a patient with such dosage form, and how to measure the *in vivo* plasma concentrations in the fasted and fed states. Specifically, the working examples teach the weight ratios of each component of the dosage form such that the pharmacokinetic parameters of the dosage form would fall within the claimed range. In particular, the disclosed range of weight ratios of the components of the hydromorphone dosage forms are relatively narrow. For example, the acrylic and methacrylic acid polymers and copolymers consist from about 60% to about 66.25% of the dosage form, and the fatty acids or fatty alcohols consist from about 23.75% to about 30% of the dosage form (*see* Exs. 17, 18 and 19). As such, Applicants submit that the specification has provided ample guidance and working examples to show one of skill in the art how to make and use the claimed invention.

In addition, since the pending claims recite the specific hydromorphone salt, hydrophobic polymer and hydrophobic fusible carrier in the dosage form, and the specification discloses a relatively narrow range of the weight ratio for each of these components, Applicants submit that claims are not as broad as the Examiner alleges. Although some experiments are need to determine other combinations or weight ratios of such components of the dosage form within the scope of the pending claims, one in the pharmaceutical field routinely engages in such experimentations. In view of the high skill level of a person of ordinary skill in the art and the guidance and working examples in the specification, Application submit that the experiments required to make and use the claimed invention are not undue.

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § is satisfied. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). As such, Applicants submit that the instant specification fully enables one of skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation, and the rejection should be withdrawn.

III. THE DOUBLE PATENTING REJECTIONS SHOULD BE WITHDRAWN

The pending claims are rejected under the judicially created doctrine of obviousness-type double patenting over various claims of U.S. Patent Nos. 5,965,161 (claims 1, 3-5, 8-21,

and 24-66) (the '161 patent), 6,335,033 (claims 1-5, 8-21, and 24-37) (the '033 patent), 6,261,599 (claims 1-8, 10-25 and 27) (the '599 patent), 6,706,281 (claims 1, 4, 7-17, 19, 22, and 24-38) (the '281 patent), 5,958,452 (claims 1-9, 10-16, 18-32, 41-50, and 62) (the '452 patent), and 6,473,442 (claims 1-8, 10-24, 27-29, and 32) (the '442 patent). The Examiner alleges that although the conflicting claims are not identical, they are not patently distinct from each other because both disclose extruded multi-particulate compositions containing hydromorphone, hydrophobic materials, and hydrophobic fusible carriers having the claimed melting point. For the following reasons, Applicants respectfully disagree.

"A non-statutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application *claim* is not patentably distinct from the reference *claim(s)* because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s)" (emphasis added). M.P.E.P. § 804(II)(B)(1) (8th Ed., Rev. 5, August 2006) (citation omitted). "When considering whether the invention defined in a *claim of an application* would have been an obvious variation of the invention defined in the *claim of a patent*, the disclosure of the patent may not be used as prior art" (emphasis added). *Id.* (citation omitted).

None of the claims in the above references cited by the Examiner anticipates or renders obvious the claimed sustained-release hydromorphone dosage form (claims 70 and 71), the method of preparing a sustained-release hydromorphone dosage form (claims 87 and 88), and the method of treating a patient with a sustained-release hydromorphone dosage form (claims 98 and 99), wherein the dosage form when containing 8 mg of hydromorphone hydrochloride will result in the claimed range of *in vivo* plasma concentrations. In particular, the cited claims of the '161 patent, '033 patent and '281 patent do not disclose or suggest any *in vivo* plasma concentration values. The cited claims of the '452 patent, '599 patent, and '442 patent also do not disclose or suggest a hydromorphone dosage form when containing 8 mg of hydromorphone hydrochloride will result in the claimed AUC and C_{max} range of *in vivo* plasma concentrations, much less a method of preparing such dosage form or a method of treating a patient with such dosage form. In fact, the '452 patent, '599 patent, and '442 patent do not have any method of treating claim.

As such, claims 70, 71, 87, 88, 98 and 99, and their respective dependent claims, are believed to be patentable over the various claims of the above references, and the double patenting rejection should be withdrawn.

CONCLUSION

It is respectfully requested that the above amendment and remarks be entered into the file of the application. Should the Examiner not agree with applicants' position, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

Date: November 3, 2008

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Enclosures

EXHIBIT A - SUMMARY OF TABLES 17-19, 24 and 26

HH-HEM Ingredients (amount / percentage)		T. 17 & 24 (Example 24)	T. 18 & 24 (Example 24)	T. 19 & 24 (Example 26)
Hydromorphone HCl (mg)		8 / (10%)	8 / 10%	8 / 10%
Eudragit RSPO (mg)		53 / (66.25%)	48 / 60%	41.5 / 51.9%
Eudragit L-100 (mg)				8.5 / 10.6%
Stearic Acid (mg)				22 / 27.5%
Stearic Alcohol (mg)		19 / 23.75%	24 / 30%	
Total Weight (mg)		80	80	80
Pharmacokinetic Data				
AUC (ng·hour/ml)	$HH\text{-}HEM_{fasted}$	19.0	19.23	15.83
	$HH\text{-}HEM_{fed}$	20.1	21.47	16.55
C_{max} (ng/ml)	$HH\text{-}HEM_{fasted}$	0.72	0.76	0.52
	$HH\text{-}HEM_{fed}$	0.75	0.93	0.65
T_{max} (hour)	$HH\text{-}HEM_{fasted}$	6.8	3.9	5.6
	$HH\text{-}HEM_{fed}$	2.4	1.9	4.1